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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ADVISORY ACTION

Status of objections and rejections

1. Applicant's response filed in the paper of 10/2/2009 is entered.

2. Claims 1, 4-5 and 13-16 are pending. Claims 2-3, 6-12 and 17-18 have been cancelled.

3. Objections to claims 4 and 5 have been withdrawn in light of claim amendment filed in the paper of 10/2/2009. Objections to claims 17 and 18 have been withdrawn in light of cancellation of claims 17 and 18 filed in the paper of 10/2/2009.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Rejection of claims 4-5 under 35 U.S.C. 112, 2^{nd} paragraph has been withdrawn in light of claim amendment filed in the paper of 10/2/2009. Rejection of claim 17 under 35 U.S.C. 112, 2^{nd} paragraph has been withdrawn in light of cancellation of claim 17 filed in the paper of 10/2/2009.

6. Rejection of claims 8 and 17-18 under 35 U.S.C. 103(a) as being unpatentable over Perlak et al. (PNAS, 88:3324-3328, April 1991, Applicant's IDS), in view of Joshi (Nucleic Acids Research, 15:9627-9640, 1987) and further in view of Dancis et al. (PNAS, 89:3869-3873, Published May 1992) is withdrawn in light cancellation of claims 8 and 17-18 filed in the paper of 10/2/2009.

Claim Objections

7. Claim 1 is objected to because of the following informalities:

Claim 1 is objected for deleting punctuation mark after "addition" in line 14. It is suggested to insert --,-- after "addition".

Claim 1 is objected for deleting "for" before "eliminating" in line 7. It is suggested to insert --for-- before "eliminating".

Objections to claim 1 have been necessitated due to the claim amendment filed in the paper of 10/2/2009.

Appropriate action/corrections are requested.

Claim Rejections - 35 USC § 103

8. Claims 1, 4-5 and 14-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Perlak et al. (PNAS, 88:3324-3328, April 1991) in view of Joshi (Nucleic Acids Research, 15:9627-9640, 1987), and further in view of Dancis et al. (PNAS, 89:3869-3873, Published May 1992) for the reasons of record stated in the Final Office action mailed 8/5/2009.

Perlak et al. teach a method of making a transgenic plant and seeds derived thereof, comprising introducing and expressing a modified heterologous coding sequence *cryIA(b)* gene of *Bacillus thuringiensis* in transgenic tobacco and tomato plants. The transgenic plants exhibited improved insect resistance. The modification did not alter the amino acid sequence of the heterologous CryIA(b) protein. The modification of coding sequence for *cryIA(b)* comprised altering AATAAA and/or ATTTA sequences. Furthermore, the modification increased G and C content throughout the region of gene to be introduced, and modification was based on plant preferred codons without changing the amino acid sequence. See in particular, page 3324, abstract; page 3324, 2nd paragraph, materials and methods (modification of the coding sequence of insect control genes) through the end of 2nd paragraph of 1st column of page 3325; page 3325, Table 1; page 3326, Figure 1, Table 2; page 3327, Figure 2, Table 3; Page 3328, 1st column, discussion.

Joshi teaches plant gene sequences having GT-rich sequences resembling animal GT-rich sequences found downstream of polyA sites. Joshi also teaches that deletion analysis in the 3' untranslated region of plant mRNA transcripts reveals a region 30 to 80 bases downstream AATAAA comprises GT rich motifs that are also required for correct and efficient polyadenylation of plant mRNA transcripts. See in particular, page 9627, abstract; page 9628, lines 16-31; pgs 9629-9631, table 1.

Perlak et al. or Joshi do not teach FRE1 from yeast.

Dancis et al. teach a nucleic acid sequence which is heterologous to a plant, and encoding yeast ferric-chelate reductase FRE1 (a protein involved in absorption of iron, a plant nutrient). The FRE1 amino acid sequence taught in the reference has 100% identity to instant SEQ ID NO: 2. The nucleic acid sequence taught in the reference comprises internal ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA, or AATAAN (wherein N is A, G, C or T) sequences and GT-rich regions which are recognized as polyadenylation signals in plants. See in particular, page 3869, abstract; page 870, figure 1; page 3873 discussion.

It would have been obvious and within the scope of an ordinary skill in the art to modify Perlak et al. method of altering a heterologous nucleic acid sequence by modifying Perlak et al. AATAAA and/or ATTTA sequences and/or Joshi's GT-rich regions present in the coding region of any non-plant heterologous sequence, and which are recognized as plant polyadenylation signal sequences, into some other sequence with a reasonable expectation of success. One of ordinary skill would have been motivated to do so for the purpose of producing a modified heterologous nucleic acid sequence which is devoid of internal polyadenylation signal sequences and encode a full-length and fully functional protein upon expression in a plant.

Given that Joshi teaches that plant GT rich regions are associated with polyadenylation process in plants, one of ordinary skill in the art would have been motivated to modify GT rich regions in said heterologous sequence to prevent premature termination of transcription with a reasonable expectation of success.

Given that Joshi clearly asserts the importance of GT rich regions in the polyadenylation of plant mRNA transcripts, it would have been obvious and within the scope of an ordinary skill in the art that any GT rich region including the one having 8 or more consecutive G or T bases would have been scanned and subsequently modified to arrive at the claimed invention with a reasonable expectation of success.

Given that Dancis et al. teach a heterologous sequence from yeast encoding FRE1 which is involved in the absorption of nutrients, it would have been obvious and within the scope of an ordinary skill in the art to modify internal AATAAA and/or ATTTA sequences, and/or GT-rich regions of Dancis et al. FRE1 coding sequence to some other sequences that are not recognized as plant polyadenylation signal sequences, using the teachings of Perlak et al. and Joshi as discussed above. One of ordinary skill in the art would have been motivated to do so for the purpose of over-expressing a full-length yeast FRE1 protein in transgenic plants to increase absorption of iron (a nutrient) in said plants with a reasonable expectation of success.

9. **Applicant's arguments & response from the examiner:**

In the paper filed 10/2/2009, Applicant argues that instantly claimed invention includes providing a FRE1 gene from yeast which is an eukaryote, whereas, Perlak et al. teach modifying a bacterial gene for introduction into plant. Applicant further argues that one of skilled in the art would not have expected that a yeast gene which is evolutionary close to plants would not be transcribed as a full length transcript upon expression in a plant. Applicant further argues that

since codon usage in yeast and plants were known to be similar, one of skilled in the art would not have expected a yeast gene to produce a truncated transcript upon expression in a plant (response, page 6, line 4 through page 7, line 4).

Applicant's arguments are carefully considered but are deemed to be unpersuasive.

It is important to note that that issue is not whether yeast is evolutionary close to plants compared to bacteria. Rather the issue is whether a non-plant gene sequence comprising internal sequences in the mRNA transcript that can be recognized as potential polyadenylation signal sequences upon expression in plants. Applicant is not on point in stating that yeast and plants have similar codon usage. Contrary to Applicant's argument, it is well documented in the art that yeast and plants (higher plants in particular, emphasis added) have different bias in codon usage.

In the instant case, Applicant's attention is drawn to figure 1 (page 3870) of Dancis et al., wherein the reference clearly teaches the complete coding sequence and the encoded FRE1 protein having 100% identity to instant SEQ ID NO: 2. The nucleic acid sequence taught in the reference is heterologous to a plant because it encodes yeast ferric-chelate reductase FRE1 (a protein involved in absorption of iron, a plant nutrient). The nucleic acid sequence taught in the reference comprises internal ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA, or AATAAN (wherein N is A, G, C or T) sequences and GT rich regions (see figure 1) which are recognized as polyadenylation signals in plants. See in particular, page 3869, abstract; page 870, figure 1; page 3873 discussion.

Applicant further argues that it is unlikely that one of ordinary skill in the art would be motivated to modify a yeast gene similarly to *Bacillus* derived gene based on the teachings of Perlak. Applicant further argues that even if one of ordinary skill in the art would have been

motivated to modify "AATAAA sequence", it is highly unlikely that one would be motivated to further modify also GT-rich sequence when a sufficient expression has been obtained by modification of "AATAAA" sequence alone (response, page 9, lines 5-11).

Applicant's arguments are carefully considered but are deemed to be unpersuasive.

Applicant's attention is drawn to Perlak et al. at page 3324, abstract; page 3324, 2nd paragraph, materials and methods (modification of the coding sequence of insect control genes) through the end of 2nd paragraph of 1st column of page 3325; page 3325, table 1; page 3326, figure 1, table 2; page 3327, figure 2, table 3; page 3328, 1st column, discussion; wherein Perlak et al. clearly teach a method of making a transgenic plant and seeds derived thereof, comprising introducing and expressing a modified coding sequence *cryIA(b)* gene of *Bacillus thuringiensis* in transgenic tobacco and tomato plants. The transgenic plants exhibited improved insect resistance. The modification did not alter the amino acid sequence of the CryIA(b) protein. The modification of coding sequence for *cryIA(b)* comprised altering AATAAA and/or ATTTA sequences. Furthermore, the modification increased G and C content throughout the region of gene to be introduced, and modification was based on plant preferred codons without changing the amino acid sequence.

It is important to note that the issue is not whether Perlak et al. should also teach GT-rich sequence as a potential polyadenylation signal in plant because Joshi does teach the role of GT-rich regions in polyadenylation in plants.

Rather, the issue is whether one of ordinary skill in the art would have known that sequences ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA, or AATAAN (wherein N is A, G, C or T) and GT rich regions present in a heterologous coding sequence would be recognized as potential polyadenylation signal sequences in plants.

Perlak et al. teachings clearly would have suggested to one of ordinary skilled in the art at the time the instantly claimed invention was made, that heterologous coding sequences (e.g. cryIA(b)) obtained from organisms other than plant comprise internal sequences such as, AATAAA or ATTTA which are recognized as polyadenylation signal sequences upon expression in a plant environment.

Likewise, Joshi's teachings would have suggested to one of ordinary skill in the art that GT regions present in a heterologous nucleic acid sequence are recognized as polyadenylation signal sequences upon expression in a plant environment. Furthermore, Perlak et al. teachings would have also provided the necessary method steps to modify said internal polyadenylation signals so that the modified heterologous nucleic acid sequence encodes the full-length protein upon expression in a plant system. For these reasons, Applicant's arguments are not on point.

Applicant while admitting that Joshi does teach GT-motifs in 3'-region are involved in addition of poly(A) in plants in plant derived genes, however argues that Joshi does not teach GT-rich sequences in heterologous genes. Applicant also argues that Joshi provides no teachings regarding the positional relation to "AATAAA sequence" in the heterologous gene. Without providing any technical reasoning, Applicant argues that it is unlikely that in a yeast derived gene, "AATAAA sequence" and GT-rich sequence would be identified as a poly(A) site by plants (response, page 8, lines 2-26; page 9, lines 1-4).

It is important to note that the issue is not whether Joshi et al. should teach a heterologous gene (e.g. yeast FRE1 in the instant case) because that deficiency is overcome by the teachings of Dancis et al. as discussed above in the rejection. Rather the issue is whether Joshi teaches GT-rich region and/or AATAAA are implicated in polyadenylation addition in plants.

Applicant attention is drawn to page 9627, abstract; page 9628, lines 16-31; pages 9629-9631, table 1, wherein Joshi clearly teaches plant gene sequences having GT-rich sequences resembling heterologous (e.g. animal) GT-rich sequences found downstream of polyA sites. Joshi also teaches that deletion analysis in the 3' untranslated region of plant mRNA transcripts reveals a region 30 to 80 bases downstream AATAAA comprises GT rich motifs that are also required for correct and efficient polyadenylation of plant mRNA transcripts. This clearly implies that Joshi does teach that GT rich motifs (or regions) and AATAAA are recognized as polyadenylation addition signals in plants.

It would have been obvious and within the scope of an ordinary skill in the art to modify the method of altering heterologous nucleic acid sequence as taught by Perlak et al. by modifying internal plant polyadenylation signals that comprises AATAAA and/or ATTTA and GT rich regions as taught by Joshi to some other sequence that are not recognized as plant polyadenylation signals.

Given that Joshi teaches that plant GT rich regions are associated with polyadenylation process in plants, one of ordinary skill in the art would have been motivated to modify GT rich regions in said heterologous sequence to prevent premature termination of transcription with a reasonable expectation of success.

Given that Joshi clearly asserts the importance of GT rich regions in the polyadenylation of plant mRNA transcripts, it would have been obvious that any GT rich region including the one having 8 or more consecutive G or T nucleotides would have been scanned and subsequently modified by an ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success.

Given that Dancis et al. teach (i) a heterologous sequence from yeast encoding FRE1 which is involved in the absorption of iron (a plant nutrient), and (ii) yeast FRE1 coding sequence which contains internal sequences, such as, ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA, or AATAAN (wherein N is A, G, C or T), and GT rich regions, and which are recognized as potential polyadenylation signals in plants as asserted by Perlak et al. and Joshi, it would have been obvious and within the scope of an ordinary skill in the art to modify said internal sequences present within Dancis et al. FRE1 coding sequence to some other sequence to prevent premature termination of transcription upon expression in a plant. One of ordinary skill in the art would have been motivated to do so for the purpose of over-expressing the full-length yeast FRE1 protein in a plant to increase absorption of iron (a nutrient) by said plant with a reasonable expectation of success.

Applicant also alleges that there can be no motivation to combine the references other than by use of impermissible hindsight. Applicant further alleges that there is not teaching or suggestions in any of the references to modify yeast FRE1 for expression in plants based on the cited references (response, paragraph bridging pages 5 and 6).

Applicant's arguments are carefully considered but are deemed to be unpersuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, given that Dancis et al. teach a heterologous

sequence from yeast encoding FRE1 which is involved in the absorption of nutrients, and given Dancis et al. FRE1 sequence contains internal sequences, such as, ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA, or AATAAN (wherein N is A, G, C or T), and GT rich regions, it would have been obvious and within the scope of an ordinary skill in the art to modify internal AATAAA and/or ATTTA sequences and/or GT-rich regions of Dancis et al. FRE1 coding sequence to some other sequences that are not recognized as polyadenylation signals in plants, using the teachings of Perlak et al. and Joshi as discussed above. One of ordinary skill in the art would have been motivated to do so for the purpose of over-expressing full-length FRE1 protein to increase absorption of iron (a nutrient) in transgenic plants with a reasonable expectation of success. Thus, one of ordinary skill in the art would have arrived at the claimed invention with a reasonable expectation of success by combining the teachings of Perlak et al., Joshi and Dancis et al. as discussed above.

Applicant is reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, given Perlak et al. and Joshi teachings when combined together would have suggested to an ordinary skill in the art that GT-rich regions in combination with AATAAA and/or ATTTA sequences were implicated in polyadenylation in plants at the time the invention was claimed, it would have been obvious to modify heterologous coding sequences having internal AATAAA and/or ATTTA sequences and GT-rich regions to prevent premature termination of the transcript when expressed in a plant with a reasonable expectation of success.

It is important to note that Obviousness does not require an absolute certainty of success but merely a reasonable expectation thereof, so long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art and this is sufficient to establish a *prima facie* case of obviousness.

Thus, it is maintained that the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

10. Claim 13 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Perlak et al. (PNAS, 88:3324-3328, April 1991) in view of Joshi (Nucleic Acids Research, 15:9627-9640, 1987), and Dancis et al. (PNAS, 89:3869-3873, Published May 1992) as applied to claims 1, 4-5, 8 and 14-17 above, and further in view of D'Halluin et al. (Plant Cell, 4:1495-1505, December 1992) for the reasons of record stated in the Final Office action mailed 8/5/2009.

Perlak et al. teachings are discussed *supra*.

Joshi's teachings are discussed *supra*.

Dancis et al. teachings are discussed *supra*.

Perlak et al., Joshi or Dancis et al. do not teach transforming a gramineae (monocotyledonous) plant.

D'Halluin et al. teach a method of transforming a maize plant. Maize is a monocotyledonous plant belonging to family gramineae. See in particular, page 1495, abstract; pgs 1503-1504, materials and methods.

It would have been obvious and within the scope of an ordinary skill in the art to over-express a modified heterologous DNA (modified by changing internal AATAAA and/or ATTTA sequences and GT rich regions to some other sequence that are not recognized as polyadenylation signals in plants as taught by Perlak et al. and Joshi) encoding any economically

important protein including yeast FRE1 protein of Dancis et al., in any plant species including an economically important maize plant using any method of plant transformation, including the plant transformation method of D'Halluin et al. One of ordinary skill in the art would have been motivated to do so for the purpose of increasing iron (important plant nutrient) absorption in said plant of gramineae family with a reasonable expectation of success.

Applicant makes similar arguments as discussed above (response page 10, lines 9-16). Accordingly the rejection is maintained.

It is noted that Applicant is arguing that claims similar in scope to the instantly pending claims were allowed in Japan (response, page 10, lines 17-20, Appendix A).

Applicant's argument was carefully considered but is deemed to be unpersuasive. It is important to note that criteria used to test for obviousness under US legal practice is different than under Japanese legal system.

Conclusions

11. Claims 1, 4-5 and 13-16 remain rejected.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VINOD KUMAR whose telephone number is (571)272-4445. The examiner can normally be reached on 8.30 a.m. to 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Vinod Kumar/
Examiner, Art Unit 1638